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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/691,654	10/24/2003	Tomoko Maeda	244295US0CONT	1300

22850 7590 03/22/2007  
OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C.  
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ALEXANDRIA, VA 22314

EXAMINER

AFREMOVA, VERA

ART UNIT

PAPER NUMBER

1657

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	03/22/2007	ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 03/22/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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<b>Office Action Summary</b>	<b>Application No.</b> 10/691,654	<b>Applicant(s)</b> MAEDA ET AL.	
	<b>Examiner</b> Vera Afremova	<b>Art Unit</b> 1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 19 December 2006.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 21,22 and 25-46 is/are pending in the application.
- 4a) Of the above claim(s) 26-44 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 21,22,25,45 and 46 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☒ Certified copies of the priority documents have been received in Application No. 09/646,899.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                 | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date: _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                        | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date: _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

Claims 21, 22 and 25 as amended and new claims 45 and 46 (12/19/2006) are under examination in the instant office action.

This application contains claims 26-44 drawn to invention(s) nonelected with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

#### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21, 22 and 25 as amended are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 is rendered indefinite by the newly inserted phrase “directly” as related to culturing cells. The meaning of this phrase is uncertain and, thus, it is unclear what protocol of cell culturing is encompassed by the newly inserted limitation.

#### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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1. Claims 21, 22 and 25 as amended and new claims 45 and 46 remain/are rejected under 35 U.S.C. 102(a) as being anticipated by Khalkhali-Ellis et al. ("Expression of macrophage markers by a population of cells obtained from synovial fluid of a subgroup of patients with juvenile rheumatoid arthritis". The Journal of Rheumatology. February 1998, Vol. 25, No. 2, pages 352-360).

Claims are directed to a method for producing osteoclast precursor cells wherein the method comprises steps of obtaining cells in a cellular fraction containing granulocytes and lymphocytes from joint fluid by centrifugation culturing the cells in an essential medium for mammalian cells with added serum and in the absence of any additional cytokine(s). Some claims are/are further drawn to culturing the cells at temperature ranging from 35-37°C in 5-7% CO<sub>2</sub> containing air for 1-3 weeks.

The cited reference by Khalkhali-Ellis et al. discloses a method for culturing cells derived from synovial or joint fluid of patients with rheumatoid arthritis wherein the method comprises steps of obtaining cell population including mononuclear cells from joint fluid by centrifugation and culturing the cells in RPMI essential medium for mammalian cells with 10% serum and in the absence of any additional cytokines. The cells are cultured at 35°C in 5 % CO<sub>2</sub> containing air for 1-3 weeks (page 353, col. 2, par. 2 and paragraph bridging page 354 and 355). The cells isolated from synovial fluid by centrifugation is a mixed cell population that contains macrophages, granulocytes and lymphocytes and, thus, the same starting cell population as claimed and when read in the light of specification (page 12). The cited method comprises identical active step(s) of culturing identical cell population under identical culture conditions for identical period of time, and, thus, the final result is reasonably considered to be identical as

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intended for the claimed method. Thus, the cited reference by Khalkhali-Ellis et al. is considered to anticipate the claimed invention.

2. Claims 21, 22 and 25 as amended and new claims 45 and 46 remain/are rejected under 35 U.S.C. 102(b) as being anticipated by Fujikawa et al. ("Human osteoclast formation and bone resorption by monocytes and synovial macrophages in rheumatoid arthritis". Annals of Rheumatic Diseases. 1996. Vol. 55, pages 816-822).

Claims as above.

The cited reference by Fujikawa et al. discloses a method for producing osteoclast precursor cells wherein the method comprises steps of obtaining cells from synovial tissue by centrifugation (page 817, col. 1, last par.) and culturing the cells in MEM (minimal essential medium) for mammalian cells with added serum and in the absence of any additional cytokines (page 817, col.2, par. 3) for at least 1 week (page 819, col. 1, par. 2, lines 12-17). Although the cited reference appears to be silent about temperature and air conditions, the claimed conditions are regular mammalian cell culture requirements. Moreover, the cells from synovial fluid were handled at temperature within the range 35-37°C (page 817, col. 1, last par.) and 5-7% CO<sub>2</sub> containing air is regular atmosphere. The cited method comprises identical active step(s) and identical structural elements as required by the claimed method. Thus, the cited reference by Fujikawa et al. is considered to anticipate the claimed invention.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

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having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 21, 22 and 25 as amended and new claims 45 and 46 remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over Khalkhali-Ellis et al. ("Expression of macrophage markers by a population of cells obtained from synovial fluid of a subgroup of patients with juvenile rheumatoid arthritis". The Journal of Rheumatology. February 1998, Vol. 25, No. 2, pages 352-360) and Fujikawa et al. ("Human osteoclast formation and bone resorption by monocytes and synovial macrophages in rheumatoid arthritis". Annals of Rheumatic Diseases. 1996. Vol. 55, pages 816-822).

Claims are above.

The cited references by Khalkhali-Ellis et al. and by Fujikawa et al. are relied upon as explained above for the disclosure of methods of culturing cells isolated from synovial tissue including synovial fluids wherein the same starting cell populations are cultured under the same conditions for the same time periods as required by the claimed method. Although the cited reference by Khalkhali-Ellis et al. is silent about the preosteoclast/osteoclast nature of cells in the final cell mixture, the reference by Fujikawa et al. explicitly teaches that the synovial mononuclear cells demonstrate development towards preosteoclast and osteoclast cells.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to culture monocytes from synovial fluid with a reasonable expectation of success in producing preosteoclast cells as adequately demonstrated by the cited references. One of skill in the art would have been motivated to obtain and/or to culture preosteoclast cells from synovial fluid for the expected benefits in determining mechanism for pathogenesis of bone destruction in the context of inflammatory disease such as rheumatoid

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arthritis. Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary. The claimed subject matter fails to patentably distinguish over the state art as represented by the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

### ***Response to Arguments***

Applicant's arguments filed 12/19/2006 have been fully considered but they are not persuasive.

With regard to the claims rejection under 35 U.S.C. 102(a) as being anticipated by Khalkhali-Ellis et al. applicants argue (response page 9) that the starting cell population or cell fraction in the method of the cited reference is not the same as required by claimed method because the protocol in Figure 1 demonstrates separation of MNCs (monocytes, lymphocytes, etc) from PMNs (granulocytes, etc. ) by Ficoll-Hypaque purification before the culturing step. However, the cited reference also teaches culturing total SF cells (all cells separated from joint fluid by centrifugation) that result in the same observations as the culturing of MNCs in the absence of PMNs, for example: see page 354, col.2, last 2 lines and page 355 col. 1, first lines. Thus, the method disclosed by the cited reference by Khalkhali-Ellis et al comprises identical active step(s) of culturing identical cell populations under identical culture conditions for identical period of time, and, thus, the final result is reasonably considered to be identical as intended for the claimed method. Therefore, the cited reference by Khalkhali-Ellis et al. is considered to anticipate the claimed invention.

With regard to the claim rejection under 35 U.S.C. 102(b) as being anticipated by Fujikawa et al. applicants argue (response page 8) that the starting cell fractions in the cited

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method is not the same as required by the claimed invention because the cited reference discloses the use of a synovial tissue not a synovial fluid for obtaining a mixed cell population as intended for further culturing and yielding precursors of osteoclasts. Yet, the claimed cell fraction identifies only 2 types of cells such as lymphocytes and granulocytes in a mixed cell population as intended for further culturing and yielding precursors of osteoclasts. It is well known that synovial tissues of rheumatoid arthritis patients are infiltrated with lymphocytes, monocytes and granulocytes. For example: see abstracts of Bond et al. (Scandinavian Journal of Immunology. 1997, Vol.46, No. 3, pages 312-6). Thus, synovial tissue and synovial fluid contain the same cells and, therefore, the starting cell populations for culturing and yielding precursors of osteoclasts in the cited method is not different from the starting cell populations as encompassed by the claimed invention.

Further, applicants' arguments with regard to the claim rejection under 35 USC § 103 are not persuasive because the reference by Fujikawa et al. explicitly teaches that the synovial mononuclear cells demonstrate development towards preosteoclast and osteoclast cells.

No claims are allowed.

### *Conclusion*

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after



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the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925.

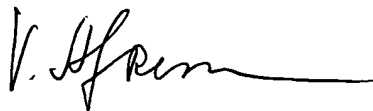
The fax phone number for the TC 1600 where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology center 1600, telephone number is (571) 272-1600.

Vera Afremova

AU 1657

March 14, 2007

A handwritten signature in dark ink, appearing to read 'V. Afremova', with a long horizontal flourish extending to the right.

VERA AFREMOVA

PRIMARY EXAMINER